

A model of morphogen transport in the presence of glypicans I

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Abstract

We analyze a one dimensional version of a model of morphogen transport, a biological process governing cell differentiation. The model was proposed by Hufnagel et al. to describe the forming of morphogen gradient in the wing imaginal disc of the fruit fly. In mathematical terms the model is a system of reaction-diffusion equations which consists of two parabolic PDE's and three ODE's. The source of ligands is modelled by a Dirac Delta. Using semigroup approach and L_1 techniques we prove that the system is well-posed and possesses a unique steady state. All results are proved without imposing any artificial restrictions on the range of parameters.

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1 Introduction

Morphogen transport (MT) is a biological process occurring in the tissues of living organisms. It is known that certain proteins (ligands) act as the morphogen - a conceptually defined substance which is responsible for the development and differentiation of cells. As it is proposed in the 'French flag model' by Wolpert [16], morphogen molecules spread from a spatially localized source through the tissue and after some time form stable concentration gradient. According to the concept of positional signalling, receptors located on the surface of the cells, detect information about local levels of morphogen concentration. This information is transmitted to nucleus and cause gene activation which finally leads to the synthesis of suitable proteins and cell differentiation. Although the role of morphogen gradient in gene expression seems to be widely accepted, the exact kinetic mechanism of its formation is still not known (see [3],[8],[9]).

Recently various models of MT, consisting of PDE-ODE systems, were proposed (see [10],[1],[4]) and analyzed (see [6],[7],[15],[13],[14]). These models assume that movement of morphogen molecules occur by different types of diffusion or by chemotaxis in the extracellular medium. Reactions with receptors (reversible binding, transcytosis) and various possibilities of degradation and internalization (of morphogens, receptors, morphogen-receptor complexes) are also being considered.

In [4] Hufnagel et al. proposed a model, which we denote [HKCS], of the formation of morphogen Wingless (Wg) in the *Drosophila Melanogaster* wing imaginal disc. Apart from mentioned before

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processes, the model takes into account interaction of Wg with glypican Dlp-like (Dlp) - protein which, similarly to receptor, interacts with morphogen through association-dissociation mechanism. Dlp molecules may also transmit Wg to each other causing the movement of morphogen particles on the surface of the wing disc. The interesting issue is the presence of a singular term (a Dirac Delta), to model the secretion of morphogen from a narrow part of the tissue which is represented in the model by a point source. In the present paper we analyze a one dimensional simplification of the [HKCS] model, which was also introduced in [4]. We intend to extend our analysis to the case of higher dimensional domains in the forthcoming article(s).

1.1 The [HKCS].1D model.

In this section we present a one dimensional simplification of the model [HKCS] introduced in [4].

For $L > 0$, $\infty \geq T > 0$, denote $I^L = (-L, L)$, $\partial I^L = \{-L, L\}$, $I_T^L = (0, T) \times I^L$, $(\partial I^L)_T = (0, T) \times \partial I^L$, $I = I^1$. The following system is of our interest:

[HKCS].1D

$$\partial_t W = D \partial_{xx}^2 W - \gamma W - [kGW - k'W^*] - [k_R RW - k'_R R^*] + s\delta, \quad (t, x) \in I_\infty^L \quad (1a)$$

$$\partial_t W^* = D^* \partial_{xx}^2 W^* - \gamma^* W^* + [kGW - k'W^*] - [k_{Rg} RW^* - k'_{Rg} R_g^*], \quad (t, x) \in I_\infty^L \quad (1b)$$

$$\partial_t R = -[k_R RW - k'_R R^*] - [k_{Rg} RW^* - k'_{Rg} R_g^*] - \alpha R + \Gamma, \quad (t, x) \in I_\infty^L \quad (1c)$$

$$\partial_t R^* = [k_R RW - k'_R R^*] - \alpha^* R^*, \quad (t, x) \in I_\infty^L \quad (1d)$$

$$\partial_t R_g^* = [k_{Rg} RW^* - k'_{Rg} R_g^*] - \alpha^* R_g^*, \quad (t, x) \in I_\infty^L \quad (1e)$$

$$\partial_x W = \partial_x W^* = 0, \quad (t, x) \in (\partial I^L)_\infty \quad (1f)$$

$$W(0) = W_0, \quad W^*(0) = W_0^*, \quad R^*(0) = R_0^*, \quad R_g^*(0) = R_{g0}^*, \quad R(0) = R_0, \quad x \in I^L \quad (1g)$$

In (1) W, G, R denote concentrations of free morphogens Wg, free glypicans Dlp and free receptors, W^*, R^* denote concentrations of morphogen-glypican and morphogen-receptor complexes, R_g^* denotes concentration of morphogen-glypican-receptor complexes. The model takes into account association-dissociation mechanism of

- W and G with rates k, k' ($kGW - k'W^*$),
- W and R with rates k_R, k'_R ($k_R RW - k'_R R^*$),
- W^* and R with rates k_{Rg}, k'_{Rg} ($k_{Rg} RW^* - k'_{Rg} R_g^*$).

Other terms of the system account for

- linear diffusion of W (W^*) with rate D (D^*): $-D \partial_{xx}^2 W$ ($-D^* \partial_{xx}^2 W^*$),
- degradation of W (W^*) with rate γ (γ^*): $-\gamma W$ ($-\gamma^* W^*$),
- internalization (endocytosis) of R (R^*, R_g^*) with rate α (α^*): $-\alpha R$ ($-\alpha^* R^*, -\alpha^* R_g^*$),
- secretion of W with rate s from the source localised at $x = 0 \in I$: $s\delta$ (δ denotes the Dirac Delta),
- production of receptors: Γ .

For simplicity we assume that G and Γ are given, strictly positive constants.

1.2 Nondimensionalisation

To analyze system [HKCS].1D we rewrite it in a nondimensional form:

$$\partial_t u_1 - \partial_{xx}^2 u_1 = -(b_1 + c_1 + u_3)u_1 + c_2 u_2 + c_4 u_4 + p_1 \delta, \quad (t, x) \in I_\infty \quad (2a)$$

$$\partial_t u_2 - d \partial_{xx}^2 u_2 = -(b_2 + c_2 + c_3 u_3)u_2 + c_1 u_1 + c_5 u_5, \quad (t, x) \in I_\infty \quad (2b)$$

$$\partial_t u_3 = -(b_3 + u_1 + c_3 u_2)u_3 + c_4 u_4 + c_5 u_5 + p_3, \quad (t, x) \in I_\infty \quad (2c)$$

$$\partial_t u_4 = -(b_4 + c_4)u_4 + u_1 u_3, \quad (t, x) \in I_\infty \quad (2d)$$

$$\partial_t u_5 = -(b_5 + c_5)u_5 + c_3 u_2 u_3, \quad (t, x) \in I_\infty \quad (2e)$$

with boundary and initial conditions

$$\begin{aligned} \partial_x u_1 &= \partial_x u_2 = 0, & (t, x) &\in (\partial I)_\infty \\ \mathbf{u}(0, \cdot) &= \mathbf{u}_0, & x &\in I \end{aligned}$$

where

$$\begin{aligned} \mathbf{u}(t, x) &= (u_1, u_2, u_3, u_4, u_5)(t, x) = K(W, W^*, R, R^*, R_g^*)(Tt, Lx), \\ \mathbf{u}_0(x) &= (u_{10}, u_{20}, u_{30}, u_{40}, u_{50})(x) = K(W_0, W_0^*, R_0, R_0^*, R_{g0}^*)(Lx), \\ T &= L^2/D, \quad K = Tk_R, \quad d = D^*/D, \\ \mathbf{b} &= (T\gamma, T\gamma^*, T\alpha, T\alpha^*, T\alpha^*), \\ \mathbf{c} &= (TkG, Tk', k_{Rg}/k_R, Tk'_R, Tk'_{Rg}), \\ \mathbf{p} &= (KTs, 0, KTT, 0, 0). \end{aligned}$$

1.3 Overview.

The aim of this paper is to establish well-posedness of (2) and the existence of a unique steady state.

During the analysis of the system (2) we encounter the following difficulties:

- absence of diffusion in equations, (2c), (2d), (2e) so that there is no smoothing effect for u_3, u_4, u_5 .
- singular source term in (2a),
- nonsymmetric zero order part of the operator for the stationary problem.

We first solve the stationary problem for (2) by using Schauder's fixed point theorem. The key observation is that the linear operator which appears in the definition of $T_n(v)$ (see proof of Theorem 1), has a diagonally dominant structure. This leads us to analyze the problem in an $L_1(I)$ setting rather than $L_2(I)$. To prove uniqueness we consider the system which is satisfied by the difference of two possible solutions and after algebraic manipulations show that it also has a diagonally dominant structure.

To remove the singularity $p_1 \delta$ from (2a) we change variables $\mathbf{z} = \mathbf{u} - \mathbf{u}^*$, where \mathbf{u}^* is the steady state to (2). Then local well-posedness in the space of continuous functions of the system for \mathbf{z} follows from the classical perturbation theory for sectorial operators. To prove global existence we notice that the quasipositivity of the vector field appearing on the right hand side of (2) guarantees that the semiflow generated by (2) preserves the positive cone. Then using compensation effects it is easy

to show that $u_3, u_4, u_5 \in L_\infty(0, T_{max}; C(I))$ and $u_1, u_2 \in L_\infty(0, T_{max}; L_1(I))$. Finally using smoothing effects of the heat semigroup we prove that $u_1, u_2 \in L_\infty(0, T_{max}; C(I))$, from which we conclude that system (2) is globally well-posed and has bounded trajectories.

Before stating the results precisely we introduce the notation and function spaces in which we will analyze the system (2).

2 Notation and function spaces

For $x, y \in \mathbb{R}, \mathbf{x}, \mathbf{y} \in \mathbb{R}^n$ we denote

$$x \vee y = \max\{x, y\}, \quad x \wedge y = \min\{x, y\}, \quad x_+ = x \vee 0, \quad x_- = (-x) \vee 0, \quad \text{sgn}(x) = \begin{cases} |x|/x & , x \neq 0 \\ 0 & , x = 0 \end{cases},$$

$$\bar{\mathbf{x}} = \max\{x_i : 1 \leq i \leq n\}, \quad \underline{\mathbf{x}} = \min\{x_i : 1 \leq i \leq n\}, \quad \langle \mathbf{x}, \mathbf{y} \rangle = \sum_{i=1}^n x_i y_i.$$

If V is a vector space we denote by V^n the n -th product power of V . If (V, \geq) is a partially ordered vector space we denote its positive cone by $V_+ := \{v \in V : v \geq 0\}$. If V, W are normed spaces we denote by $\mathcal{L}(V, W)$ the space of linear, bounded operators from V to W with the usual uniform convergence topology. We put $\mathcal{L}(V) = \mathcal{L}(V, V)$.

We make standard convention that C denotes a positive constant which depends on various parameters which are specified explicitly in the text.

To analyze the problem we will use the following Banach spaces

$$\begin{aligned} X &= X_0 = C(\bar{I}), \quad X_1 = C_N^2(\bar{I}) = \{u : u \in C^2(\bar{I}), \quad u'(-1) = u'(1) = 0\}, \\ X_{1/2} &= C^{0,1}(I) = \text{Lip}(I) = W_\infty^1(I), \\ Y &= Y_0 = L_1(I), \quad Y_1 = W_{1,N}^2(I) = \{u : u \in W_1^2(I), u'(-1) = u'(1) = 0\}, \\ Y_{1/2} &= W_1^1(I) = AC(I). \end{aligned}$$

Notice that due to the imbedding $W_1^2(I) \subset C^1(\bar{I})$ the boundary conditions in the definition of Y_1 are meaningful.

3 Results

From now on we assume that

$$d, \mathbf{b} > 0, \quad \mathbf{c}, \mathbf{p} \geq 0, \quad \mathbf{u}_0 \in X_+^5.$$

We start with the analysis of the stationary problem and prove that there exists unique nonnegative steady state. Observe that due to the absence of diffusion in (2c),(2d),(2e) the stationary problem reduces to the system (19) (see below) of two semilinear elliptic equations for u_1^* and u_2^* .

Theorem 1. *System (2) possesses a unique nonnegative steady state $\mathbf{u}^* \in X_{1/2} \times X_1 \times X_{1/2}^3$ such that*

$$u_3^* = H(u_1^*, u_2^*), \quad b_4 u_4^* = k_1 u_1^* H(u_1^*, u_2^*), \quad b_5 u_5^* = k_2 u_2^* H(u_1^*, u_2^*), \quad (3a)$$

where

$$k_1 = b_4/(b_4 + c_4), \quad k_2 = c_3 b_5/(b_5 + c_5), \quad H(x_1, x_2) = p_3/(k_1 x_1 + k_2 x_2 + b_3) \quad (4)$$

and (u_1^*, u_2^*) is a solution of the following boundary value problem

$$-u_1^{*''} + (b_1 + c_1 + k_1 H(u_1^*, u_2^*))u_1^* - c_2 u_2^* = p_1 \delta, \quad x \in I \quad (5a)$$

$$-du_2^{*''} - c_1 u_1^* + (b_2 + c_2 + k_2 H(u_1^*, u_2^*))u_2^* = 0, \quad x \in I, \quad (5b)$$

$$u_1^{*'} = u_2^{*'} = 0, \quad x \in \partial I. \quad (5c)$$

i.e. for every $\varphi \in X_{1/2}$

$$\int_I [u_1^{*'} \varphi' + ((b_1 + c_1 + k_1 H(u_1^*, u_2^*))u_1^* - c_2 u_2^*) \varphi] = s_1 \varphi(0)$$

and (5b) is satisfied in the classical sense. Moreover

$$u_1^* + p_1 |x|/2 \in X_1. \quad (6)$$

A typical shape of the steady state is to be found in Figure 1.

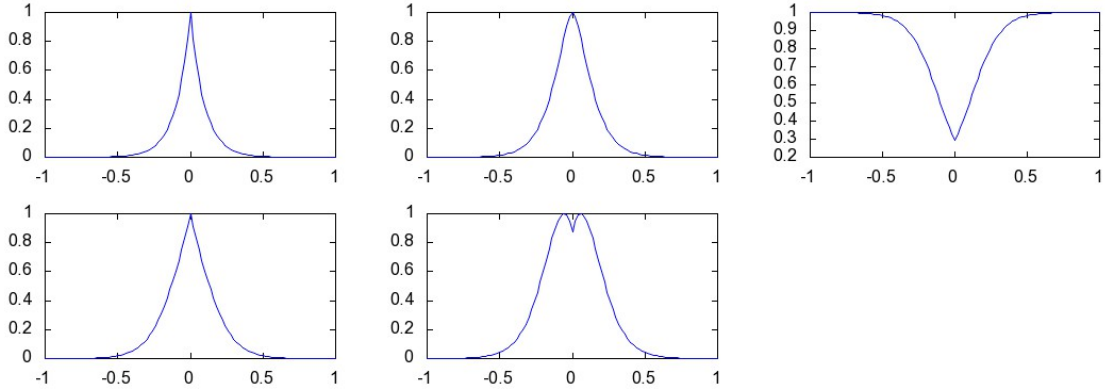


Figure 1: Graph of \mathbf{u}^* (normalised to 1) computed for the following values of parameters: $\mathbf{b} = [100, 10, 10, 10, 10]$, $\mathbf{c} = [10, 10, 1, 10, 10]$, $\mathbf{p} = [100, 0, 100, 0, 0]$, $d = 1/10$. First row - $u_1^*/\|u_1^*\|_X, u_2^*/\|u_2^*\|_X, u_3^*/\|u_3^*\|_X$, second row - $u_4^*/\|u_4^*\|_X, u_5^*/\|u_5^*\|_X$. Notice the surprising difference in behavior of u_4^* and u_5^* near $x = 0$ (see Remark (1) for explanation).

In the following remark we analyze the behavior of the stationary solution near the source of morphogen.

Remark 1 (\mathbf{u}^* near $x = 0$). Observe that as \mathbf{u}^* is unique it must be even. Indeed otherwise $\mathbf{u}^*(-x)$ would be a second solution as the system (5) is invariant under the transformation $x \rightarrow -x$. Thus using (6)

$$(u_1^*)'(0^+) = -p_1/2 < 0, \quad (7a)$$

$$(u_2^*)'(0) = 0, \quad (7b)$$

where $(u_1^*)'(0^+)$ denotes the right-sided derivative of u_1^* at $x = 0$.

Using (3) and (7) we compute directly

$$(u_3^*)'(0^+) = \frac{p_1 k_1}{2p_3} [H(u_1^*(0), u_2^*(0))]^2 > 0, \quad (8a)$$

$$(u_4^*)'(0^+) = -\frac{p_1 k_1 k_2}{2p_3 b_4} [H(u_1^*(0), u_2^*(0))]^2 (u_2^*(0) + b_3/k_2) < 0, \quad (8b)$$

$$(u_5^*)'(0^+) = \frac{p_1 k_1 k_2}{2p_3 b_5} [H(u_1^*(0), u_2^*(0))]^2 u_2^*(0) > 0. \quad (8c)$$

In particular from (8b), (8c) and the fact that \mathbf{u}^* is even we infer that $u_4(0)$ ($u_5(0)$) is a strict local maximum (minimum), which explains the difference near $x = 0$ in u_4^* (steep spike) and u_5^* (depletion effect) as observed in Figure (1).

Next we turn our attention to the evolution problem and establish its well-posedness and the uniform boundedness of trajectories in X^5 .

Theorem 2. *System (2) possesses a unique, global in time, nonnegative solution*

$$u_1 \in C([0, \infty); X) \cap C^1((0, \infty); X) \cap C((0, \infty); X_{1/2}) \quad (9a)$$

$$u_2 \in C([0, \infty); X) \cap C^1((0, \infty); X) \cap C((0, \infty); X_1) \quad (9b)$$

$$u_3, u_4, u_5 \in C^1([0, \infty); X) \quad (9c)$$

such that for every $\varphi \in X_{1/2}, t \in (0, \infty)$

$$\int_I \partial_t u_1 \varphi + D \int_I \partial_x u_1 \partial_x \varphi = \int_I [-(b_1 + c_1 + u_3)u_1 + c_2 u_2 + c_4 u_4] \varphi + p_1 \varphi(0)$$

and other equations are satisfied in the sense of X . Moreover $\mathbf{u} \in L_\infty(0, \infty; X^5)$ and the following estimates hold

$$\sum_{i=3}^5 u_i(t) \leq e^{-\underline{\mathbf{b}}t} \sum_{i=3}^5 u_{i0} + p_3(1 - e^{-\underline{\mathbf{b}}t})/\underline{\mathbf{b}}, \quad (10a)$$

$$\sum_{i \in \{1,2,4,5\}} \|u_i(t)\|_Y \leq e^{-\underline{\mathbf{b}}t} \sum_{i \in \{1,2,4,5\}} \|u_{i0}\|_Y + p_1(1 - e^{-\underline{\mathbf{b}}t})/\underline{\mathbf{b}}. \quad (10b)$$

We conclude with a remark concerning the discussion about the asymptotic behavior.

Remark 2 (Asymptotics). For the case of morphogen Dpp acting in the imaginal wing disc of the fruit fly without the presence of glypicans, it is proved in [6] that the morphogen gradient (i.e. steady state of the appropriate evolution system) is globally exponentially stable. It is expected that an analogous result should hold for [HKCS].1D, though we are not able to prove even the local stability of the steady state. However it may also be the case that the presence of glypicans within a certain range of parameters has a destabilising effect on the equilibrium.

4 Lemmas

In this section we collect lemmas which are used in the proofs of the results. The first lemma concerns well-posedness of the abstract ODE's in Banach spaces, while the second states that realisations of one dimensional Laplace operator in the chosen Banach spaces are sectorial. Since these lemmas are well known we state them only to make the article more self-contained. For the proofs we refer the interested reader to [11], chapter 6.1 and [12], chapter 3.1.

Lemma 1. *Assume that*

1. $V_1 \subset V$ are arbitrary, densely imbedded Banach spaces.
2. $A : V \supset V_1 \rightarrow V$ is a sectorial operator.
3. $F : V \rightarrow V$ is Lipschitz on bounded subsets.

Then for given $v_0 \in V$, the Cauchy problem

$$v' - Av = F(v), \quad t > 0 \quad (11a)$$

$$v(0) = v_0 \quad (11b)$$

has a unique, strong, maximal solution

$$v \in C([0, T_{max}); V) \cap C^1((0, T_{max}); V) \cap C((0, T_{max}); V_1).$$

The following Duhamel formula holds

$$v(t) = e^{At}v_0 + \int_0^t e^{A(t-s)}F(v(s))ds, \quad t \in [0, T_{max}).$$

Moreover T_{max} is characterised by the following blow-up condition:

$$T_{max} < \infty \text{ implies } \limsup_{t \rightarrow T_{max}^-} \|v(t)\|_V = \infty. \quad (12)$$

In particular if there exists $C > 0$ such that for $t \in [0, T_{max})$

$$\|F(v(t))\|_V \leq C(\|v(t)\|_V + 1), \quad (13)$$

then $T_{max} = \infty$.

For $Z \in \{X, Y\}$ we define the Z -realisation of the Laplace operator with Neumann boundary conditions on I :

$$A_Z : Z \supset Z_1 \rightarrow Z, \quad A_Z u = u'', \quad u \in Z_1$$

Lemma 2. *A_Z is a sectorial, densely defined operator with compact resolvent. It generates an analytic, strongly continuous semigroup e^{tA_Z} and for $t > 0$ the following estimates hold*

$$\|e^{tA_Z}\|_{\mathcal{L}(Z)} \leq 1, \quad \|e^{tA_Y}\|_{\mathcal{L}(Y, X)} \leq C(1 \wedge t)^{-1/2}.$$

Moreover (A_X, e^{tA_X}) is a restriction of (A_Y, e^{tA_Y}) to X i.e.

$$A_X u = A_Y u, \quad u \in X_1, \quad e^{tA_X} u = e^{tA_Y} u, \quad (t, u) \in [0, \infty) \times X.$$

The third lemma concerns solvability of linear elliptic systems with diagonally dominant zero order term. It is crucial in the proofs of existence and uniqueness of the steady state of the system (2).

Lemma 3. *Assume that for $i, j = 1, 2$, $d_i > 0$, $a_{ij} \in X_+$ and*

$$a_{11} - a_{21} \geq 0, \quad (14a)$$

$$a_{22} - a_{12} \geq 0. \quad (14b)$$

Define operators

$$\begin{aligned} M : Y^2 &\rightarrow Y^2, \quad Mu = (-a_{11}u_1 + a_{12}u_2, a_{21}u_1 - a_{22}u_2), \\ G : Y^2 &\supset Y_1^2 \rightarrow Y^2, \quad G = (d_1A_Y) \times (d_2A_Y) + M. \end{aligned}$$

Then G is a sectorial, densely defined operator with a compact resolvent $R(\lambda, G) = (\lambda - G)^{-1}$ and the following hold

$$(0, \infty) \subset \rho(G) \text{ and } \|R(\lambda, G)\|_{\mathcal{L}(Y^2)} \leq 1/\lambda, \quad (15a)$$

$$\|R(\lambda, G)\|_{\mathcal{L}(Y^2, Y_1^2)} \leq C(1 + 1/\lambda), \quad (15b)$$

$$R(\lambda, G) \text{ preserves } Y_+^2, \quad (15c)$$

where $\lambda > 0$ and C depends only on $d_i, \|a_{ij}\|_X$.

Proof. To prove that G is sectorial and has a compact resolvent notice that it is a perturbation of the operator $(d_1A_Y) \times (d_2A_Y)$ having these two properties by a bounded operator $M \in \mathcal{L}(Y^2)$. From the compactness of the resolvent of G we get that the spectrum $\sigma(G)$ only contains eigenvalues (Theorem 6.29 [5]).

In the rest of the proof we will use the following observation. Let $\gamma : \mathbb{R} \rightarrow \mathbb{R}$ be a function such that $x\gamma(x) \geq 0$, $|\gamma| \leq 1$. Then using (14) we obtain the following pointwise inequality

$$\left\langle Mu, (\gamma(u_1), \gamma(u_2)) \right\rangle = -a_{11}u_1\gamma(u_1) + a_{12}u_2\gamma(u_1) + a_{21}u_1\gamma(u_2) - a_{22}u_2\gamma(u_2) \quad (16a)$$

$$= -u_1\gamma(u_1)(a_{11} - a_{21}\gamma(u_2)\gamma(u_1)) - u_2\gamma(u_2)(a_{22} - a_{12}\gamma(u_1)\gamma(u_2)) \leq 0. \quad (16b)$$

Choose $\lambda > 0$, $f \in Y^2$, $u \in Y_1^2$ such that

$$f = (\lambda - G)u. \quad (17)$$

To prove (15a) we estimate

$$\begin{aligned} \|f\|_{Y^2} &\geq \int_I \left\langle f, (\operatorname{sgn}(u_1), \operatorname{sgn}(u_2)) \right\rangle = \lambda\|u\|_{Y^2} - \sum_{i=1}^2 d_i \int_I u_i'' \operatorname{sgn}(u_i) \\ &\quad - \int_I \left\langle Mu, (\operatorname{sgn}(u_1), \operatorname{sgn}(u_2)) \right\rangle \geq \lambda\|u\|_{Y^2}, \end{aligned}$$

where we used (16) with $\gamma = \operatorname{sgn}$ and the following Kato's inequality (see Lemma 2 in [2])

$$- \int_I v'' \operatorname{sgn}(v) \geq 0, \quad v \in Y_1. \quad (18)$$

To prove (15b) observe that from (17), (15a) we have

$$\|Gu\|_{Y^2} \leq \|f\|_{Y^2} + \lambda\|u\|_{Y^2} \leq 2\|f\|_{Y^2},$$

whence

$$\begin{aligned}
\|u\|_{Y_1^2} &\leq C(\|(A_Y u_1, A_Y u_2)\|_{Y^2} + \|u\|_{Y^2}) \leq C[(d_1 \wedge d_2)^{-1} \|Gu - Mu\|_{Y^2} + \|f\|_{Y^2}/\lambda] \\
&\leq C[(d_1 \wedge d_2)^{-1} (\|Gu\|_{Y^2} + \|M\|_{\mathcal{L}(Y^2)} \|u\|_{Y^2}) + \|f\|_{Y^2}/\lambda] \\
&\leq C[(d_1 \wedge d_2)^{-1} (2 + \|M\|_{\mathcal{L}(Y^2)}/\lambda) + 1/\lambda] \|f\|_{Y^2} \\
&\leq C(1 + 1/\lambda) \|f\|_{Y^2},
\end{aligned}$$

Finally to prove (15c) assume that $f \in Y_+^2$. Let $\phi(x) = (\text{sgn}(x) - 1)/2$. Then $-1 \leq \phi(x) \leq 0$ and $x\phi(x) = x_-$. Using (16) with $\gamma = \phi$ and (18) we obtain

$$\begin{aligned}
0 &\geq \int_I \langle f, (\phi(u_1), \phi(u_2)) \rangle = \lambda \sum_{i=1}^2 \int_I u_i \phi(u_i) - \frac{1}{2} \sum_{i=1}^2 d_i \int_I u_i'' \text{sgn}(u_i) - \int_I \langle Mu, (\phi(u_1), \phi(u_2)) \rangle \\
&\geq \lambda \|u_-\|_{Y^2},
\end{aligned}$$

whence $u \geq 0$. □

5 Proof of Theorem 1

We divide the proof into two parts. To prove existence of a solution of (5) we first approximate the singular source term $p_1 \delta$ by more regular functions $h_n \in Y_+$. Using Schauder's fixed point theorem we prove solvability of the approximated problem. Finally using compactness methods we show that the approximated solutions converge to a solution of (5). In the proof of uniqueness we show that the difference of any two possible steady states belongs to the kernel of a certain operator $\lambda - G$, where $\lambda > 0$ and G satisfies assumptions of Lemma (3).

5.1 Existence

Choose a sequence $h_n \in Y_+$ such that $h_n \rightharpoonup^* \delta$ in $\mathcal{M}([-1, 1])$ - the space of signed Radon measures. For $\mathbf{v} \in X_+^2$ consider the following problem

$$-u_1'' + (b_1 + c_1 + k_1 H(v_1, v_2))u_1 - c_2 u_2 = p_1 h_n, \quad x \in I \quad (19a)$$

$$-du_2'' - c_1 u_1 + (b_2 + c_2 + k_2 H(v_1, v_2))u_2 = 0, \quad x \in I, \quad (19b)$$

$$u_1' = u_2' = 0, \quad x \in \partial I, \quad (19c)$$

where H is defined in (4). Using notation introduced in Lemma (3) system (19) is equivalent to

$$(\lambda - G)(u_1, u_2) = (p_1 h_n, 0),$$

where

$$\begin{aligned}
\lambda &= \underline{\mathbf{b}}, \\
d_1 &= 1, d_2 = d, \\
a_{11} &= b_1 - \underline{\mathbf{b}} + c_1 + k_1 H(v_1, v_2), & a_{12} &= c_2, \\
a_{21} &= c_1, & a_{22} &= b_2 - \underline{\mathbf{b}} + c_2 + k_2 H(v_1, v_2).
\end{aligned}$$

Observe that condition (14) holds, thus using Lemma (3) we obtain that (19) has a unique solution $(u_1, u_2) \in Y_{1,+}^2$ and there exists C_1 which do not depend on $(v_1, v_2), (u_1, u_2), h_n$ such that

$$\|(u_1, u_2)\|_{Y_1^2} \leq C_1 \|h_n\|_Y. \quad (20)$$

Using the compact imbedding

$$Y_1 \subset\subset X \quad (21)$$

and (20) we obtain that there exists C_2 such that

$$\|(u_1, u_2)\|_{X^2} \leq C_2 \|(u_1, u_2)\|_{Y_1^2} \leq C_1 C_2 \|h_n\|_Y. \quad (22)$$

Define

$$\begin{aligned} V_n &= \{(v_1, v_2) \in X_+^2 : \|(v_1, v_2)\|_{X^2} \leq C_1 C_2 \|h_n\|_Y\}, \\ T_n : V_n &\rightarrow V_n, \quad T_n(v_1, v_2) = (u_1, u_2), \end{aligned}$$

where (u_1, u_2) is the solution of (19). Observe that V_n is a closed and convex subset of a Banach space X^2 and T_n is well defined, compact (because of (21),(22)) and continuous (because H is a globally Lipschitz continuous function on \mathbb{R}_+^2). Hence by Schauder's theorem T_n has a fixed point $(u_{n,1}^*, u_{n,2}^*) \in V_n$.

Since $(h_n)_{n=1}^\infty$ is bounded in Y we get, by (22), that $(u_{n,1}^*, u_{n,2}^*)_{n=1}^\infty$ is bounded in Y_1^2 . From the imbeddings $Y_1 \subset X_{1/2} \subset\subset X$ there exist $(u_1^*, u_2^*) \in X_{1/2}$ and a subsequence $(u_{n_k,1}^*, u_{n_k,2}^*)_{k=1}^\infty$ such that for $i = 1, 2$

$$\begin{aligned} (u_{n_k,i}^*)' &\rightharpoonup^* (u_i^*)', \text{ in } L_\infty(I) \\ u_{n_k,i}^* &\rightarrow u_i^*, \text{ in } X. \end{aligned}$$

Fix $\varphi \in X_{1/2}$, then since $T_{n_k}(u_{n_k,1}^*, u_{n_k,2}^*) = (u_{n_k,1}^*, u_{n_k,2}^*)$ we have:

$$\int_I (u_{n_k,1}^*)' \varphi' + [(b_1 + c_1 + k_1 H(u_{n_k,1}^*, u_{n_k,2}^*)) u_{n_k,1}^* - c_2 u_{n_k,2}^*] \varphi = s_1 \int_I h_{n_k} \varphi, \quad (23a)$$

$$d \int_I (u_{n_k,2}^*)' \varphi' + [-c_1 u_{n_k,1}^* + (b_2 + c_2 + k_2 H(u_{n_k,1}^*, u_{n_k,2}^*)) u_{n_k,2}^*] \varphi = 0, \quad (23b)$$

Using again the fact that H is globally Lipschitz continuous on \mathbb{R}_+^2 we can pass in (23) with $n_k \rightarrow \infty$ and obtain that (u_1^*, u_2^*) is a solution of (19).

5.2 Uniqueness

Assume that $(u_1, u_2), (v_1, v_2)$ are two solutions of (5). Noting $z_i = u_i - v_i$ for $i = 1, 2$ we have:

$$\begin{aligned} -z_1'' + (b_1 + c_1)z_1 - c_2 z_2 + k_1(H(u_1, u_2)u_1 - H(v_1, v_2)v_1) &= 0 \\ -dz_2'' - c_1 z_1 + (b_2 + c_2)z_2 + k_2(H(u_1, u_2)u_2 - H(v_1, v_2)v_2) &= 0 \end{aligned}$$

Define

$$\begin{aligned} D &= (k_1 u_1 + k_2 u_2 + b_3)(k_1 v_1 + k_2 v_2 + b_3) \\ w_i &= (u_i + v_i)/2, \quad i = 1, 2 \end{aligned}$$

and compute

$$\begin{aligned}
u_1 v_2 - u_2 v_1 &= z_1(u_2 + v_2)/2 - z_2(u_1 + v_1)/2 = z_1 w_2 - z_2 w_1 \\
H(u_1, u_2)u_1 - H(v_1, v_2)v_1 &= p_3 \left(\frac{u_1}{k_1 u_1 + k_2 u_2 + b_3} - \frac{v_1}{k_1 v_1 + k_2 v_2 + b_3} \right) = \frac{p_3}{D} (k_2(u_1 v_2 - u_2 v_1) + b_3 z_1) \\
&= \frac{p_3}{D} ((k_2 w_2 + b_3)z_1 - k_2 w_1 z_2) \\
H(u_1, u_2)u_2 - H(v_1, v_2)v_2 &= p_3 \left(\frac{u_2}{k_1 u_1 + k_2 u_2 + b_3} - \frac{v_2}{k_1 v_1 + k_2 v_2 + b_3} \right) = \frac{p_3}{D} (-k_1(u_1 v_2 - u_2 v_1) + b_3 z_2) \\
&= \frac{p_3}{D} (-k_1 w_2 z_1 + (k_1 w_1 + b_3)z_2).
\end{aligned}$$

Thus

$$\begin{aligned}
-z_1'' + (b_1 + \frac{k_1 p_3 b_3}{D} + c_1 + \frac{k_1 k_2 p_3 w_2}{D})z_1 - (c_2 + \frac{k_1 k_2 p_3 w_1}{D})z_2 &= 0 \\
-dz_2'' - (c_1 + \frac{k_1 k_2 p_3 w_2}{D})z_1 + (b_2 + \frac{k_2 p_3 b_3}{D} + c_2 + \frac{k_1 k_2 p_3 w_1}{D})z_2 &= 0
\end{aligned}$$

Hence, using the notation introduced in Lemma (3), (z_1, z_2) belongs to the kernel of the operator $\underline{\mathbf{b}} - G$ where

$$\begin{aligned}
d_1 &= 1, d_2 = d \\
a_{11} &= b_1 - \underline{\mathbf{b}} + \frac{k_1 p_3 b_3}{D} + c_1 + \frac{k_1 k_2 p_3 w_2}{D}, & a_{12} &= c_2 + \frac{k_1 k_2 p_3 w_1}{D}, \\
a_{21} &= c_1 + \frac{k_1 k_2 p_3 w_2}{D}, & a_{22} &= b_2 - \underline{\mathbf{b}} + \frac{k_2 p_3 b_3}{D} + c_2 + \frac{k_1 k_2 p_3 w_1}{D}.
\end{aligned}$$

Since nonnegativity of w_1, w_2 ensures that assumption (14) is fulfilled we infer that $z_1 = z_2 = 0$ which finishes the proof.

5.3 Regularity of u_1^* outside $x = 0$.

Observe that $E = -p_1|x|/2$ satisfies $-E'' = p_1\delta$ in the sense of distributions. Owing to (5a) $v = u_1^* - E$ solves the following boundary value problem

$$\begin{aligned}
-v'' &= f, & x &\in I \\
v' &= -E', & x &\in \partial I
\end{aligned}$$

with $f = c_2 u_2^* - (b_1 + c_1 + k_1 H(u_1^*, u_2^*))u_1^*$. Since $f \in X$ then (6) follows.

6 Proof of Theorem 2

Using the theory of analytic semigroups we first establish the local well-posedness of (2). Using quasipositivity of the right hand side of (2) we next prove that the generated semiflow preserves nonnegativity of initial conditions. Then using a compensation effect we derive $L_\infty(0, \infty, X)$ estimate for u_3, u_4, u_5 and $L_\infty(0, \infty, Y)$ estimate for u_1, u_2 . Finally thanks to the regularising properties of the semigroup $e^{A_\nu t}$ we bootstrap the estimate to $\mathbf{u} \in L_\infty(0, \infty, X^5)$.

6.1 Local existence

We rewrite system (2) in the new variables $\mathbf{z} = \mathbf{u} - \mathbf{u}^*$, where \mathbf{u}^* is the unique steady state of (2), and put it into the semigroup framework:

$$\mathbf{z}' - \mathbf{A}_X \mathbf{z} = \mathbf{f}(\mathbf{z}), \quad t > 0 \quad (24a)$$

$$\mathbf{z}(0) = \mathbf{z}_0 = \mathbf{u}_0 - \mathbf{u}^*, \quad (24b)$$

where

$$\mathbf{A}_X = A_X \times (dA_X) \times 0^3$$

$$\mathbf{f} = (f_1, f_2, f_3, f_4, f_5) : X^5 \rightarrow X^5$$

$$f_1(\mathbf{z}) = -(b_1 + c_1)z_1 - (z_1 z_3 + u_1^* z_3 + u_3^* z_1) + c_2 z_2 + c_4 z_4$$

$$f_2(\mathbf{z}) = -(b_2 + c_2)z_2 - c_3(z_2 z_3 + u_3^* z_2 + u_2^* z_3) + c_1 z_1 + c_5 z_5$$

$$f_3(\mathbf{z}) = -b_3 z_3 - (z_1 z_3 + u_1^* z_3 + u_3^* z_1) - c_3(z_2 z_3 + u_3^* z_2 + u_2^* z_3) + c_4 z_4 + c_5 z_5$$

$$f_4(\mathbf{z}) = -(b_4 + c_4)z_4 + (z_1 z_3 + u_1^* z_3 + u_3^* z_1)$$

$$f_5(\mathbf{z}) = -(b_5 + c_5)z_5 + c_3(z_2 z_3 + u_3^* z_2 + u_2^* z_3).$$

Observe that \mathbf{A}_X generates an analytic, strongly continuous semigroup in X^5 :

$e^{t\mathbf{A}_X} = e^{tA_X} \times e^{tdA_X} \times (Id)^3$. Moreover \mathbf{f} is Lipschitz continuous on bounded subsets of X^5 . Using Lemma (1) we obtain that (24) possesses a unique solution defined on a maximal time interval $[0, T_{max})$ with the following regularity:

$$\begin{aligned} z_1, z_2 &\in C([0, T_{max}); X) \cap C^1((0, T_{max}); X) \cap C((0, T_{max}); X_1) \\ z_3, z_4, z_5 &\in C^1([0, T_{max}); X). \end{aligned}$$

Setting $\mathbf{u} = \mathbf{z} + \mathbf{u}^*$ it is obvious that \mathbf{u} is the unique solution to (2).

6.2 Positive cone invariance

Consider the following system

$$\partial_t v_1 - \partial_{xx}^2 v_1 = -(b_1 + c_1 + (v_3)_+)v_1 + c_2(v_2)_+ + c_4(v_4)_+ + p_1 \delta, \quad (t, x) \in I_\infty \quad (25a)$$

$$\partial_t v_2 - d\partial_{xx}^2 v_2 = -(b_2 + c_2 + c_3(v_3)_+)v_2 + c_1(v_1)_+ + c_5(v_5)_+, \quad (t, x) \in I_\infty \quad (25b)$$

$$\partial_t v_3 = -(b_3 + (v_1)_+ + c_3(v_2)_+)v_3 + c_4(v_4)_+ + c_5(v_5)_+ + p_3, \quad (t, x) \in I_\infty \quad (25c)$$

$$\partial_t v_4 = -(b_4 + c_4)v_4 + (v_1)_+(v_3)_+, \quad (t, x) \in I_\infty \quad (25d)$$

$$\partial_t v_5 = -(b_5 + c_5)v_5 + c_3(v_2)_+(v_3)_+, \quad (t, x) \in I_\infty \quad (25e)$$

with boundary and initial conditions

$$\begin{aligned} \partial_x v_1 &= \partial_x v_2 = 0, & (t, x) &\in (\partial I)_\infty \\ \mathbf{v}(0, \cdot) &= \mathbf{u}_0, & x &\in I \end{aligned}$$

Reasoning as in the previous section, the system (25) possesses a unique maximally defined solution $\mathbf{v}(t)$ on $[0, T'_{max})$ in X^5 . We will now prove that $\mathbf{v}(t) \geq 0$ for $t \in [0, T'_{max})$. Multiplying (25) by

$-(\mathbf{v})_-$ and adding equations we obtain:

$$d/dt \sum_{i=1}^5 \|(v_i)_-\|_2^2 + \|\partial_x(v_1)_-\|_2^2 + 2d\|\partial_x(v_2)_-\|_2^2 \leq 0$$

$$\sum_{i=1}^5 \|(v_i(0))_-\|_2^2 = 0.$$

Thus $\mathbf{v}(t) \geq 0$ for $t \in [0, T'_{max})$. Then $\mathbf{v}_+ = \mathbf{v}$ and it readily follows from (25) that \mathbf{v} solves (2) on $[0, T'_{max})$. Consequently, $\mathbf{v} = \mathbf{u}$ on $[0, T'_{max})$ and $T'_{max} \leq T_{max}$. Finally observe that if $T'_{max} < \infty$ then, by (12), $\limsup_{t \rightarrow T'_{max}} \|\mathbf{u}(t)\|_{X^5} = \limsup_{t \rightarrow T'_{max}} \|\mathbf{v}(t)\|_{X^5} = \infty$ thus $T'_{max} = T_{max}$ and $\mathbf{u}(\mathbf{t}) \geq 0$ on $[0, T_{max})$.

6.3 $u_3, u_4, u_5 \in L_\infty(0, T_{max}; X)$

Adding equations (2c),(2d),(2e) and using nonnegativity of \mathbf{u} , we obtain for every $x \in I$

$$\partial_t \sum_{i=3}^5 u_i + \underline{b} \sum_{i=3}^5 u_i \leq p_3, \quad t \in [0, T_{max}).$$

Thus

$$0 \leq \sum_{i=3}^5 u_i \leq e^{-bt} \sum_{i=3}^5 u_{i0} + p_3(1 - e^{-bt})/\underline{b}, \quad t \in [0, T_{max}). \quad (26)$$

6.4 $T_{max} = \infty$

Observe that, due to (26), $\mathbf{f}(\mathbf{z}(\mathbf{t}))$ satisfies (13) with $V = X^5$ hence $T_{max} = \infty$ by Lemma (1) .

6.5 $u_1, u_2 \in L_\infty(0, \infty; Y)$

After integrating equations (2a), (2b), (2d), (2e) over the set I and adding them together we obtain

$$\frac{d}{dt} \left(\sum_{i \in \{1,2,4,5\}} \|u_i\|_Y \right) + \underline{b} \sum_{i \in \{1,2,4,5\}} \|u_i\|_Y \leq p_1,$$

Thus

$$\sum_{i \in \{1,2,4,5\}} \|u_i(t)\|_Y \leq e^{-bt} \sum_{i \in \{1,2,4,5\}} \|u_{i0}\|_Y + p_1(1 - e^{-bt})/\underline{b}. \quad (27)$$

6.6 $u_1, u_2 \in L_\infty(0, \infty; X)$

From (26), (27) we obtain that $f_1(\mathbf{z}) + z_1 \in L_\infty(0, \infty; Y)$. Using the Duhamel formula and estimates from Lemma (2) we get

$$\begin{aligned} \|z_1(t)\|_X &\leq e^{-t} \|e^{tA_X}\|_{\mathcal{L}(X)} \|z_{10}\|_X + \int_0^t e^{-s} \|e^{sA_Y}\|_{\mathcal{L}(Y,X)} \|f_1(\mathbf{z}(t-s)) + z_1(t-s)\|_Y ds \\ &\leq \|z_{10}\|_X + C \int_0^\infty (1 \wedge s)^{-1/2} e^{-s} ds \|f_1(\mathbf{z}) + z_1\|_{L_\infty(Y)} \leq \|z_{10}\|_X + C \|f_1(\mathbf{z}) + z_1\|_{L_\infty(Y)}, \end{aligned}$$

whence $u_1 \in L_\infty(0, \infty; X)$. A similar argument gives $u_2 \in L_\infty(0, \infty; X)$ and completes the proof.

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